(FILE 'HOME' ENTERED AT 14:41:16 ON 06 FEB 2002)

FILE 'EUROPATFULL, PCTFULL, USPATFULL, USPAT2, WPIDS' ENTERED AT 14:41:58
ON 06 FEB 2002
L1 259 S BIPHOSPHONATE#
L2 1572 S L1 OR ALENDRONATE OR IBANDRONATE OR RISEDRONATE OR ?DRONATE
L3 1 S L2(20A)PHOSPHOLIPID
L4 3 S L2(S)PHOSPHOLIPID

FILE 'MEDLINE, EMBASE, BIOSIS' ENTERED AT 14:49:30 ON 06 FEB 2002

FILE 'CAPLUS' ENTERED AT 14:49:38 ON 06 FEB 2002
L5 4 S L4

FILE 'MEDLINE, EMBASE, BIOSIS' ENTERED AT 14:53:19 ON 06 FEB 2002
L6 12 S L4
L7 6 DUP REM L6 (6 DUPLICATES REMOVED)

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=> d his

     (FILE 'HOME' ENTERED AT 11:51:00 ON 28 APR 2003)

     FILE 'EUROPATFULL, PATDPAFULL, PCTFULL, USPATFULL, USPAT2, WPIDS'
ENTERED
     AT 11:51:27 ON 28 APR 2003
L1          1313 S ALENDRONATE OR RISEDRONATE OR TILUDRONATE OR IBANDRONATE
L2            17 S L1(S)(NSAID)
```

L5 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:789614 CAPLUS
DOCUMENT NUMBER: 134:290229
TITLE: Effect of bisphosphonates on surface hydrophobicity and phosphatidylcholine concentration of rodent gastric mucosa
AUTHOR(S): Lichtenberger, Lenard M.; Romero, Jimmy J.; Gibson, George W.; Blank, Marion A.
CORPORATE SOURCE: Department of Integrative Biology & Pharmacology, The University of Texas Medical School at Houston, Houston, TX, 77030, USA
SOURCE: Dig. Dis. Sci. (2000), 45(9), 1792-1801
CODEN: DDSCDJ; ISSN: 0163-2116
PUBLISHER: Kluwer Academic/Plenum Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE
FORMAT

AB Bisphosphonates are a family of chem. related zwitterionic mols. that are used clin. to retard bone resorption in individuals with osteoporosis and assocd. skeletal diseases. Inflammation and ulceration of the upper gastrointestinal tract by a mechanism that relates to a topical irritant action is assocd. with the consumption of some bisphosphonates. In the present study, the authors investigated the effects of 3 bisphosphonate mols., pamidronate, alendronate, and risedronate on the surface hydrophobicity and phosphatidylcholine (PC) concn. of the antral mucosa. The authors also examd. how these surface changes related to mucosal injury in an established rat model, in which the test compds. were administered in combination with indomethacin. The authors initially detd. that a combination of pamidronate (300 mg/kg) and indomethacin (40 mg/kg) induced a redn. in mucosal surface hydrophobicity and macroscopic lesion formation by 15 min and mucosal PC concn. by 30 min, with the magnitude of these changes increasing over the 4-h study period. An equivalent dose of alendronate or risedronate in combination with indomethacin produced modest or no macroscopic injury, resp., to the antral mucosa over the 4-h study, although the bisphosphonates clearly induced surface injury and some glandular necrosis when examd. at the light microscopic level. These bisphosphonates also induced modest decreases in antral surface hydrophobicity and mucosal PC concn. that appeared to be related to their injurious potential. In conclusion, the variable toxicity of bisphosphonates to the antral mucosa appears to be assocd. with their ability to compromise the surface hydrophobic **phospholipid** barrier of the tissue, with **pamidronate** > > > **alendronate** > **risedronate**. This bisphosphonate effect on the surface barrier may trigger the development of mucosal injury and possible ulceration.

ACCESSION NUMBER: 94365426 MEDLINE
DOCUMENT NUMBER: 94365426 PubMed ID: 8083541
TITLE: Liposome mediated depletion of macrophages: mechanism of action, preparation of liposomes and applications.
AUTHOR: Van Rooijen N; Sanders A
CORPORATE SOURCE: Department of Cell Biology, Faculty of Medicine, Free University, Amsterdam, Netherlands.
SOURCE: JOURNAL OF IMMUNOLOGICAL METHODS, (1994 Sep 14) 174 (1-2) 83-93. Ref: 56
Journal code: IFE; 1305440. ISSN: 0022-1759.
PUB. COUNTRY: Netherlands
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199410
ENTRY DATE: Entered STN: 19941021
Last Updated on STN: 19941021
Entered Medline: 19941012

AB Selective depletion of macrophages from tissues in vivo can be used to investigate whether these cells are playing a role in defined biological processes. This question is particularly relevant to various host defense mechanisms. We have developed a macrophage 'suicide' technique, using the liposome mediated intracellular delivery of dichloromethylene-bisphosphonate (Cl2MBP or **clodronate**). The method is specific with respect to phagocytic cells of the mononuclear phagocyte system (MPS) for the following reasons: (1) The natural fate of liposomes is phagocytosis. (2) Once ingested by macrophages, the **phospholipid** bilayers of the liposomes are disrupted under the influence of lysosomal phospholipases. (3) Cl2MBP intracellularly released in this way does not easily escape from the cell by crossing the cell membranes. (4) Cl2MBP released in the circulation from dead macrophages or by leakage from liposomes, will not easily enter non-phagocytic cells and has an extremely short half life in the circulation and body fluids. In the present review, the preparation of Cl2MBP-liposomes has been described in detail. Furthermore, the mechanism of action of the new approach and its applicabilities are discussed.

AB . . . host defense mechanisms. We have developed a macrophage 'suicide' technique, using the liposome mediated intracellular delivery of dichloromethylene-bisphosphonate (Cl2MBP or **clodronate**). The method is specific with respect to phagocytic cells of the mononuclear phagocyte system (MPS) for the following reasons: (1) The natural fate of liposomes is phagocytosis. (2) Once ingested by macrophages, the **phospholipid** bilayers of the liposomes are disrupted under the influence of lysosomal phospholipases. (3) Cl2MBP intracellularly released in this way does. .

L3 ANSWER 1 OF 1 PCTFULL COPYRIGHT 2002 MicroPatent

ACCESSION NUMBER: 2001076577 PCTFULL EW 200142 ED 20011030

TITLE (ENGLISH): UNIQUE COMPOSITIONS OF ZWITTERIONIC PHOSPHOLIPIDS AND BISPHOSPHONATES AND USE OF THE COMPOSITIONS AS BISPHOSPHATE DELIVERY SYSTEMS WITH REDUCED GI TOXICITY

TITLE (FRENCH): COMPOSITIONS UNIQUES DE PHOSPHOLIPIDES ZWITTERIONIQUES ET DE BISPHOSPHONATES ET LEUR UTILISATION SOUS FORME DE SYSTEMES D'ADMINISTRATION DE BISPHOSPHATES PRESENTANT UNE TOXICITE GASTRO-INTESTINALE LIMITEE

INVENTOR(S): LICHTENBERGER, Lenard, M.

PATENT ASSIGNEE(S): THE BOARD OF REGENTS OF THE UNIVERSITY OF TEXAS SYSTEM

AGENT: STROZIER, Robert, W.

LANGUAGE OF PUBL.: English

LANGUAGE OF FILING: English

DOCUMENT TYPE: Patent

PATENT INFORMATION:

| NUMBER | KIND | DATE |
|---|---|---|
| WO 2001076577 | A2 | 20011018 |

DESIGNATED STATES: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG UZ VN YU ZW GH GM KE LS MW MZ SD SL SZ TZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE TR BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG

APPLICATION INFO.: WO 2001-US11375 20010406

PRIORITY (ORIGINAL): US 2000-60/195562 20000407

ACCESSION NUMBER: 1999009991 PCTFULL
TITLE (ENGLISH): NOVEL AMIDE DERIVATIVES
TITLE (FRENCH): DERIVES AMIDES
INVENTOR(S): FUNAMIZU, Hidenori; ISHIYAMA, Nobuo; IKEGAMI, Satoru; OKUNO, Tadashi; INOGUCHI, Kiyoshi; HUANG, Ping; LOEW, Gilda, H.
PATENT ASSIGNEE(S): KAKEN PHARMACEUTICAL CO., LTD.; MOLECULAR RESEARCH INSTITUTE
LANGUAGE OF PUBL.: English
LANGUAGE OF FILING: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

| NUMBER | KIND | DATE |
|---|---|---|
| WO 9909991 | A1 | 19990304 |

DESIGNATED STATES: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW GH GM KE LS MW SD SZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG
APPLICATION INFO.: WO 1998-US17232 19980820
PRIORITY (ORIGINAL): US 1997-08/916575 19970822

L11 ANSWER 9 OF 21 PCTFULL COPYRIGHT 2002 MicroPatent
ACCESSION NUMBER: 1999004773 PCTFULL
TITLE (ENGLISH): METHOD FOR INHIBITING BONE RESORPTION
TITLE (FRENCH): PROCEDE D'INHIBITION DE RESORPTION OSSEUSE
INVENTOR(S): DAIFOTIS, Anastasia, G.; SANTORA, Arthur, C., II; YATES, A., John
PATENT ASSIGNEE(S): MERCK & CO., INC.
LANGUAGE OF PUBL.: English
LANGUAGE OF FILING: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

| NUMBER | KIND | DATE |
|---|---|---|
| WO 9904773 | A2 | 19990204 |

DESIGNATED STATES: AL AM AU AZ BA BB BG BR BY CA CN CU CZ EE GE HR HU ID IL IS JP KG KR KZ LC LK LR LT LV MD MG MK MN MX NO NZ PL RO RU SG SI SK SL TJ TM TR TT UA US UZ VN YU GH GM KE LS MW SD SZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG
APPLICATION INFO.: WO 1998-US14796 19980717
PRIORITY (ORIGINAL): US 1997-60/053351 19970722
US 1997-60/053.535 19970723
GB 1997-9717590.5 19970820
GB 1997-9717850.3 19970822

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     (FILE 'HOME' ENTERED AT 14:41:16 ON 06 FEB 2002)

     FILE 'EUROPATFULL, PCTFULL, USPATFULL, USPAT2, WPIDS' ENTERED AT
14:41:58
     ON 06 FEB 2002
L1           259 S BIPHOSPHONATE#
L2          1572 S L1 OR ALENDRONATE OR IBANDRONATE OR RISEDRONATE OR ?DRONATE
L3             1 S L2(20A)PHOSPHOLIPID
L4             3 S L2(S)PHOSPHOLIPID

     FILE 'MEDLINE, EMBASE, BIOSIS' ENTERED AT 14:49:30 ON 06 FEB 2002

     FILE 'CAPLUS' ENTERED AT 14:49:38 ON 06 FEB 2002
L5             4 S L4

     FILE 'MEDLINE, EMBASE, BIOSIS' ENTERED AT 14:53:19 ON 06 FEB 2002
L6            12 S L4
L7             6 DUP REM L6 (6 DUPLICATES REMOVED)

     FILE 'EUROPATFULL, PCTFULL, USPATFULL, USPAT2, WPIDS' ENTERED AT
15:02:26
     ON 06 FEB 2002
L8           493 S L2(S)OSTEOPOROSIS
L9           193 S L8(L)(GI OR GASTROINTESTIN?)
L10           72 S L9(L)TOXIC?
L11           21 S L10 NOT PY>=2000
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ethenylidenebisphosphonate, tetra-n-propyl ethenyli.shy.
denebisphosphonate, tetraheptyl ethenylidenebisphosphonate, dimethyl diethyl ethenylidenebisphophonate, dibutyl dimethyl ethenylidenebisphosphonate, methyl tributyl ethenylidene.shy. **bisphosphonate** or ethyl tri-n-hexyl ethenylidenebisphosphonate.

Substantially . . . part, with an equivalent amount of tetramethyl ethenylidenebisphosphonate, tetraethyl ethenylidenebisphosphonate, tetra-n-propyl ethenylidenebisphosphonate, tetraheptyl ethenylidenebisphosphonate, dimethyl diethyl ethenylidenebisphosphonate, dibutyl dimethyl ethenylidene.shy. **bisphosphonate**, methyl tributyl ethenylidenebisphosphonate or ethyl tri-n-hexyl ethenylidenebisphosphonate.

Substantially . . . is replaced, in whole or in part, with an equivalent amount of tetramethyl ethenylidenebisphosphonate, tetraethyl ethenylidenebisphosphonate, tetra-n-propyl ethenylidenebisphosphonate, tetraheptyl ethenylidene.shy. **bisphosphonate**, dimethyl diethyl ethenylidenebisphosphonate, dibutyl dimethyl ethenylidenebisphosphonate, methyl tributyl ethenylidenebisphosphonate or ethyl tri-n-hexyl ethenylidenebisphosphonate.

CLMEN. . . amount of the amine is from about 10 to about 20 mole percent and the amount of the tetraalkyl methylene **bisphosphonate** is from about 10 to about 20 mole percent.

ACCESSION NUMBER: 221611 EUROPATFULL EW 198720 FS OS STA B
TITLE: Antimicrobial agents and process for their manufacture.
Antimikrobielle Mittel und Verfahren zu ihrer Herstellung.
Agents antimicrobiens et leur procede de preparation.
INVENTOR(S): Degenhardt, Charles Raymond, 10555 Wellingwood Court, Cincinnati Ohio 45240, US;
Charbonneau, Duane Larry, 7820 Devonshire Drive, West Chester Ohio 45069, US
PATENT ASSIGNEE(S): THE PROCTER & GAMBLE COMPANY, One Procter & Gamble Plaza, Cincinnati Ohio 45202, US
PATENT ASSIGNEE NO: 200173
AGENT: Ernst, Hubert, et al, PROCTER & GAMBLE EUROPEAN TECHNICAL CENTER Temselaan 100, B-1820 Strombeek-Bever, BE
OTHER SOURCE: ESP1987016 EP 0221611 A2 870513
SOURCE: Wila-EPZ-1987-H20-T1
DOCUMENT TYPE: Patent
LANGUAGE: Anmeldung in Englisch; Veroeffentlichung in Englisch
DESIGNATED STATES: R AT; R BE; R CH; R DE; R ES; R FR; R GR; R IT; R LI; R LU; R NL; R SE
PATENT INFO.PUB.TYPE: EPA2 EUROPAEISCHE PATENTANMELDUNG
PATENT INFORMATION:

| PATENT NO | KIND | DATE |
|---|---|---|
| EP 221611 | A2 | 19870513 |
| 'OFFENLEGUNGS' DATE: | | 19870513 |
| APPLICATION INFO.: EP 1986-201890 | | 19861028 |
| PRIORITY APPLN. INFO.: US 1985-795306 | | 19851104 |
| US 1986-855877 | | 19860423 |

DETDEN It has been found that certain novel tetraalkyl ethenylidene.shy. **bisphosphonates** are effective against a broad spectrum of gram-.shy. positive and gram-negative microorganisms, such as bacteria, yeasts, viruses, fungi and protozoa,. . .
The compounds suitable for conversion to tetraalkyl ethenylidenebisphosphonates include tetraalkyl methylene.shy. **bisphosphonates** (mixtures of these compounds may be used). As used herein, the term tetraalkyl methylenebisphosphonate refers to compounds having the formula:. . .
Typically, . . . 20 to about 96 mole percent of formaldehyde. Preferably, from about 10 to about 20 mole percent of tetraalkyl methylene **bisphosphonate** is combined with from about 10 to about 20 mole percent of the amine and from about 50 to about. . .
The . . . ethylene oxide content, forming a mix.shy. ture of ether-esters.
17. Vegetable waxes including carnauba and candelilla waxes.
18. **Phospholipids**, such as lecithin and derivatives.
19. Sterols. Cholesterol, cholesterol fatty acid esters are examples thereof.
20. Amides, such. . .
The . . . about 10,000 mg/kg per day, preferably from about 1 mg/kg to about 250 mg/kg per day, of a tetraalkyl ethenylidene.shy. **bisphosphonate** described herein. This amount can be given in a single dose or multiple doses repeatedly or sustained release dosages over. . .
6.95g . . . refluxed for 46 hours. After the methanol is eliminated as des.shy. cribed above in Example I, 4.72g of tetran-butyl ethenylidene.shy. **bisphosphonate** is produced as a clear liquid.
A . . . amount of tetramethyl ethenylidenebisphosphonate, tetraethyl

effective in the treatment of Paget's disease, hypercalcemia of malignancy, osteolytic lesions produced by bone metastases, and bone loss due to immobilization or sex hormone deficiency. These same **bisphosphonates** are then tested in the resorption pit assay described above to confirm a correlation between their known utility and positive. . .

ACCESSION NUMBER: 528586 EUROPATFULL EW 199508 FS PS STA B
TITLE: Inhibiting osteoclast-mediated bone resorption using aminoalkyl-substituted phenyl derivatives.
Verhinderung der durch Osteoklasten verursachten Knochenresorption durch aminoalkylsubstituierte Phenylderivate.
Inhibition de la resorption osseuse causee par osteoclastes utilisant de derives phenylique substituee par aminoalkyl.

INVENTOR(S): Egbertson, Melissa S., 1232 Lois Road, Ambler, PA 19002,
US;
Gould, Robert J., 973 Gravel Pike, Green Lane, PA 18054,
US;
Hartman, George D., 1529 Tennis Circle, Lansdale, PA 19446, US
PATENT ASSIGNEE(S): MERCK & CO. INC., 126, East Lincoln Avenue P.O. Box 2000, Rahway New Jersey 07065-0900, US
PATENT ASSIGNEE NO: 200479
AGENT: Barrett-Major, Julie Diane et al, Merck & Co., Inc. European Patent Department Terlings Park Eastwick Road, Harlow Essex CM20 2QR, GB
AGENT NUMBER: 50911

OTHER SOURCE: EPB1995015 EP 0528586 B1 950222
SOURCE: Wila-EPS-1995-H08-T1
DOCUMENT TYPE: Patent
LANGUAGE: Anmeldung in Englisch; Veroeffentlichung in Englisch
DESIGNATED STATES: R CH; R DE; R FR; R GB; R IT; R LI; R NL
PATENT INFO.PUB.TYPE: EPB1 EUROPAEISCHE PATENTSCHRIFT
PATENT INFORMATION:

| PATENT NO | KIND | DATE | | |
|---|---|---|---|---|
| EP 528586 | B1 | 19950222 | | |
| 'OFFENLEGUNGS' DATE: | | 19930224 | | |
| APPLICATION INFO.: EP 1992-307156 | | 19920805 | | |
| PRIORITY APPLN. INFO.: US 1991-743475 | | 19910809 | | |
| REFERENCE PAT. INFO.: EP 85321 | A | EP 272671 | A | |
| EP 437367 | A | EP 478328 | A | |


DETDEN. . . systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of **phospholipids**, such as cholesterol, stearylamine or phosphatidylcholines.

The . . . systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of **phospholipids**, such as cholesterol, stearylamine or phosphatidylcholines.

The . . . Sato, M., et al., Journal of Bone and Mineral Research, Vol. 5, No. 1, 1990. That article teaches that certain **bisphosphonates** have been used clinically and appear to be effective in the treatment of Paget's disease, hypercalcemia of malignancy, osteolytic lesions produced by bone metastases, and bone loss due to immobilization or sex hormone deficiency. These same **bisphosphonates** are then tested in the resorption pit assay described above to confirm a correlation between their known utility and positive. . .

The . . . Sato, M., et al., Journal of Bone and Mineral Research, Vol. 5, No. 1, 1990. That article teaches that certain **bisphosphonates** have been used clinically and appear to be

L5 ANSWER 7 OF 12 USPATFULL

| | |
|---|---|
| ACCESSION NUMBER: | 1999:19135 USPATFULL |
| TITLE: | Methods for the treatment of arthritis using phosphonates and NSAIDS |
| INVENTOR(S): | Hovancik, Kristine, Binghamton, NY, United States<br>Francis, Marion David, Cincinnati, OH, United States<br>Underwood, Richard Allen, Hamilton, OH, United States |
| PATENT ASSIGNEE(S): | The Proctor & Gamble Company, Cincinnati, OH, United States (U.S. corporation) |

| | NUMBER | KIND | DATE |
|---|---|---|---|
| PATENT INFORMATION: | US 5869471 | | 19990209 |
| APPLICATION INFO.: | US 1995-479787 | | 19950607 (8) |

RELATED APPLN. INFO.: Continuation of Ser. No. US 1994-212376, filed on 11 Mar 1994, now abandoned which is a continuation of Ser. No. US 1992-906726, filed on 30 Jun 1992, now abandoned

| | |
|---|---|
| DOCUMENT TYPE: | Utility |
| FILE SEGMENT: | Granted |
| PRIMARY EXAMINER: | Henley, III, Raymond |
| LEGAL REPRESENTATIVE: | Clark, Karen F., McMahon, Mary Pat, Winter, William J. |
| NUMBER OF CLAIMS: | 24 |
| EXEMPLARY CLAIM: | 1 |
| LINE COUNT: | 2517 |

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM The administration of **NSAIDs** and bone-active phosphonates has been suggested as a method for enhancing the anti-inflammatory activity of **NSAIDs**. Such treatments using **bisphosphonates** and **NSAIDs** are disclosed in the following references, all hereby incorporated by reference herein, U.S. Pat. Nos. 4,269,828, to Flora, et al.. . .